3
Tumors of the Salivary Glands

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Introduction

Pathologists generally agree that histologic grading of some malignant salivary gland tumors is predictive of their clinical behavior (1,2). However, the data on the clinical utility of grading all salivary tumors are incomplete (Barnes et al., 2005). In addition, subjectivity of grading and interobserver variation appear to limit the impact of tumor grading.

Many malignant salivary gland tumors are considered either low- or high-grade malignancies, and are not graded (Silverberg et al., 2006). These 2 groups of tumors include the following microscopic forms of salivary carcinomas:

- **Low-grade malignant salivary gland tumors.** This group includes polymorphous low-grade adenocarcinoma (Figure 3-1), basal cell adenocarcinoma (Figure 3-2), acinic cell carcinoma (Figure 3-3), clear cell adenocarcinoma, epithelial-myoepithelial carcinoma, and cystadenocarcinoma.

- **High-grade malignant salivary gland tumors.** This group comprises relatively less common tumors, such as salivary duct carcinoma, squamous cell carcinoma, adenosquamous carcinoma, oncocytic carcinoma, sebaceous carcinoma, and undifferentiated large cell or small cell carcinomas.

The remaining malignant tumors, such as mucoepidermoid carcinoma, adenocarcinoma not otherwise specified (NOS), adenoid cystic carcinoma, and malignant mixed tumors, are graded according to generally accepted criteria.

Mucoepidermoid Carcinoma

Mucoepidermoid carcinoma (MEC) is the most common malignant salivary gland tumor (3,4). The primary sites include the parotid gland (50%) and minor salivary glands of the palate (20%), and less commonly the buccal mucosa, lips, retromolar region, and tongue. In a significant number of patients with this type, there is a history of radiation to the head and neck area.

While pathologists generally agree that MEC grading is an important prognostic factor, there is a lack of consensus regarding the histopathologic criteria that are most useful. Grading is dependent on many factors, either alone or in combination, including:

- Proportion of cystic spaces filled with mucus, as compared to solid areas of tumor. Low-grade tumors are typically cystic and contain mucus in the dilated lumina.
- Relative proportion of cell types. MEC are composed of 4 cell types: intermediate squamous cells, clear cells, keratinizing squamous cells, and mucus-secreting goblet cells, and their proportion varies among tumors.
- Degree of invasiveness. Low-grade tumors are characterized by a circumscribed growth, whereas intermediate and high-grade ones are overtly invasive.
- Pattern of invasion, and the presence of vascular and perineural invasion.
- Mitotic rate, cellular atypia, and necrosis. These signs of malignancy are found in high-grade tumors.
- Tumor site. It has been shown that grading MEC of the submandibular gland does not correlate with the biologic behavior of the tumor, as compared to tumors from other sites.

According to the system proposed by Goode et al. (3) and endorsed in the monograph of the Armed Forces Institute of Pathology (Ellis and Auclair, 1996), MEC is best graded on a scale from 1 to 3 and classified as a low-grade, intermediate-grade, or high-grade tumor, as follows (Figure 3-4):
• **Low-grade mucoepidermoid carcinoma.** This tumor typically contains cystic spaces that are filled with mucin. Tumor nest are composed of intermediate squamous or clear cells, keratinizing squamous cells, and mucin-producing cells. The intermediate cells predominate, but the goblet cells are also prominent and often produce large amounts of mucin. The tumors are usually well circumscribed and lack invasiveness.

• **Intermediate-grade mucoepidermoid carcinoma.** This tumor is predominantly solid, and cystic spaces do not account for more than 20% of the total mass. The tumor is composed predominantly of intermediate cells, but there are also keratinizing squamous cells, clear cells, and easily identifiable mucin-producing goblet cells. There is more pronounced nuclear anaplasia, and foci of necrosis may be found. These tumors are clearly invasive, and one may also find vascular or neural invasion.

• **High-grade mucoepidermoid carcinoma.** This tumor is almost entirely solid and does not contain cystic areas. It is mostly composed of intermediate squamous and clear cells, and may resemble nonkeratinizing squamous cell carcinoma. Scattered mucin-secreting cells may be seen, especial in slides stained with mucin.

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<thead>
<tr>
<th>Table 3-1. Histological parameters for grading mucoepidermoid carcinoma and point values for each grade.</th>
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<tr>
<td><strong>Microscopic parameters</strong></td>
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<tr>
<td>Intracystic component &gt;20%</td>
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<tr>
<td>Neural invasion present</td>
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<tr>
<td>Necrosis present</td>
</tr>
<tr>
<td>Mitoses &gt;4 per 10 high-power fields (hpf)</td>
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<tr>
<td>Anaplasia</td>
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<td><strong>Grade</strong></td>
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<tr>
<td>Low grade</td>
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<td>Intermediate grade</td>
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<td>High grade</td>
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*Source: Modified from Ellis and Auclair, 1996.*

**Figure 3-1.** Polymorphous low-grade adenocarcinoma. This tumor is composed of tubular and trabecular components.

**Figure 3-2.** Basal cell adenocarcinoma. This tumor is composed of relatively uniform basaloïd small blue cells, arranged into solid nests. At the periphery of the tumor nests, the cells appear palisaded.

**Figure 3-3.** Acinic cell carcinoma. The solid sheets of cells in this tumor have a well-developed cytoplasm containing cytoplasmic granules.
Figure 3-4. Mucoepidermoid carcinoma. A. A low-grade MEC is composed of cystic tumor islands. B. An intermediate-grade MEC has solid and cystic nests. Cystic spaces account for less than 20% of the total area. C. A high-grade MEC has tumor cells that form solid nests and contain only scattered mucin-secreting goblet cells.

carmine or p-aminosalicylic acid. Nuclei are vesicular and contain prominent nucleoli; anaplasia may be also seen. There is brisk mitotic activity (4 or more/10 hpf). While necrosis may be present, it is rarely extensive.

Comments
1. DNA analysis is somewhat helpful, especially for high-grade MEC, which is usually aneuploid.
2. Testing for proliferation markers may be of some added prognostic value, but it is not routinely recommended (5).
3. As pointed out by Rosai (2004), marked nuclear atypia, frequent mitoses, and extensive necrosis are not typical of mucoepidermoid carcinoma of any grade.

Adenocarcinoma, Not Otherwise Specified

This tumor type accounts for approximately 15% of all malignant salivary gland tumors. It is composed of tubular, ductular, or glandular structures that do not show any distinct resemblance to other salivary gland tumors (Figure 3-5). Hence, the diagnosis is usually reached by exclusion.

The grading is based on the degree of cytologic atypia, nuclear anaplasia, ductulo-glandular differentiation, the presence of mitoses and necrosis (Ellis and Auclair, 1996). Accordingly, adenocarcinomas NOS are graded as low-, intermediate-, and high-grade tumors (6). The essential features of this 3-tiered grading are summarized in Table 3-2.
Figure 3-5. Adenocarcinoma, NOS. This moderately differentiated tumor shows tubule formation, but contains numerous solid nests and cords.

Adenoid Cystic Carcinoma

Adenoid cystic carcinoma is the most common malignant tumor of minor salivary glands, but it also occurs in the major salivary glands (7,8). Despite a tendency to grow slowly, it is highly invasive and tends to spread along the nerves or metastasize to the lungs. Tumor location has an impact on the prognosis: those arising in minor salivary glands have a worse prognosis than those in major salivary glands.

Three main histologic patterns are recognized: cribriform, tubular, and solid (Figure 3-6). In tumors with a mixed growth pattern, a solid component with more than 30% of the tumor is indicative of a poor prognosis.

Adenoid cystic carcinoma can be graded as well differentiated, moderately differentiated, and poorly differentiated, as follows:

- **Well-differentiated adenoid cystic carcinoma.** Typically, this tumor has a tubular pattern and is composed of tubules or nests enclosed by hyaline material.
- **Moderately differentiated adenoid cystic carcinoma.** This tumor grows in a cribriform pattern and consists of nests and cords of tumor cells, with multiple cyst-like spaces resembling ductal lumina (“Swiss-cheese” pattern).
- **Poorly differentiated adenoid cystic carcinoma.** This tumor exhibits a solid pattern of growth and is composed of anaplastic tumor cells forming solid nests or sheets. Inside the solid nests, areas of comedo-like necrosis may be evident.

Malignant Mixed Tumor

Malignant mixed tumors most often develop due to the malignant transformation of a preexisting benign mixed tumor, but may also arise de novo as malignant biphasic tumors without a preexisting benign neoplasia (9,10). The rate of malignant transformation is approximately 8% (10).

- **Carcinoma ex pleomorphic adenoma.** This tumor typically contains a benign component that has all the features of a mixed salivary gland tumor. Tumors undergoing malignant transformation show more prominent mitotic activity, contain broad areas of hyalinization, and are usually larger than typical mixed tumors. The malignant component has the features of high-grade adenocarcinoma, but the mesenchymal-like component appears benign. Occasionally, the malignant component may have the microscopic

<table>
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<tr>
<th>Features</th>
<th>Low Grade</th>
<th>Intermediate Grade</th>
<th>High Grade</th>
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<tr>
<td>Nuclear morphology</td>
<td>Mostly uniform</td>
<td>Mild pleomorphism; nucleoli evident</td>
<td>Hyperchromatic; show pleomorphism</td>
</tr>
<tr>
<td>Mitoses</td>
<td>Rare</td>
<td>Easily found</td>
<td>Abundant</td>
</tr>
<tr>
<td>Necrosis</td>
<td>Absent</td>
<td>Occasional</td>
<td>Always present</td>
</tr>
<tr>
<td>Ductulo glandular-</td>
<td>Prominent</td>
<td>Present but solid nests abound</td>
<td>Few or no ducts; tumor</td>
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<td>differentiation</td>
<td></td>
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<td>composed of solid nests and cords</td>
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Source: Modified from Ellis and Auclair, 1996.
features of a low-grade carcinoma, such as polymorphous low-grade adenocarcinoma or basal cell adenocarcinoma, and such tumors have a better prognosis than the high-grade adenocarcinomas arising in mixed tumors. All carcinomas arising in preexisting benign tumors can be classified as localized or frankly invasive. Localized tumors have a better prognosis. Small areas of malignancy—those less than 8 mm in diameter—also have a better prognosis than larger lesions.

• **Primary malignant mixed tumor.** These tumors are also called carcinosarcomas, because both the epithelial and the mesenchymal-like components show microscopic signs of malignancy (11,12). The epithelial and mesenchymal components apparently stem from the same neoplastic clones (12).

These tumors are highly aggressive and have a poor prognosis.

**References**

**Books and Monographs**


Articles